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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,856	VOLLMERS, PHILLIP	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-32,34-42 and 48-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-32,34-42 and 48-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/23/10 has been entered.

2. The examiner of the application has changed. This case has now been transferred. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Lynn Bristol, Group Art Unit 1643.

3. Claims 27-32, 34-42 and 48-54 are all the pending claims.

4. Claims 27, 31 and 43 were amended and new claims 52-54 were added in the Response of 7/23/10.

5. Claims 27-32, 34-42 and 48-54 are all the pending claims for this application.

6. This Office Action contains new grounds for objection and rejection.

Information Disclosure Statement

7. The IDS of 7/23/10 has been considered and entered. The initialed and signed 1449 form is attached.

Priority

8. It is noted that the instant application has been filed as a 371 application of PCT/DE2004/002503. The instant application is found to obtain benefit to the PCT application because the inventorship has been corrected as set forth below. The inventors on PCT/DE2004/002503 are Heinz Vollmers and Hans Konrad Muller-Hermelink. The inventor of the instant application has been changed to Heinz Vollmers.

Inventorship

9. In view of the papers filed 7/23/10, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a)(2). The inventorship of this application has been changed by substituting the inventor name from "Philip Vollmers" to "Heinz Peter Vollmers".

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Withdrawal of Objections

Oath/Declaration

10. The objection to the oath or declaration because the signature is not in permanent ink, or its equivalent in quality, as required under 37 CFR 1.52(a)(1)(iv) is withdrawn.

Applicants have filed a legible oath/declaration with the Response of 7/23/10.

Specification

11. The objection to Figure 5 for reading as "For the stains shown in Figure 9 Figure 5" is withdrawn.

Applicant has amended this portion of the text in the Response of 7/23/10 to delete reference to Figure 9.

Withdrawal of Rejections

Claim Rejections - 35 USC § 102

12. The rejection of Claims 27-43 and 48-51 under 35 U.S.C. 102(b) as being anticipated by EP 1 531 162 A1 (Vollmers et al., May 18, 2005) is withdrawn.

Vollmers (Heinz) et al. teach an antibody which is identical to that of SEQ ID NO:1 and 3 of the instant application. The inventorship has been properly changed in the instant application with the filing of the Rule 1.48(a) request and the Rule 1.48(a)(5) request on 7/23/10, and therefore, the rejection is withdrawn.

13. The rejection of Claims 27-43 and 48-51 under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter is withdrawn.

The instant application claims benefit to a PCT application DE2004/002503 for which the Applicant is Heinz Vollmers. The inventorship has been properly changed in the instant application with the filing of the Rule 1.48(a) request and the Rule 1.48(a)(5) request on 7/23/10, and therefore, the rejection is withdrawn.

Objections Maintained

Specification

14. The objection to the disclosure because of following informalities set forth in the Office Action of 3/23/10 is maintained:

"The description of Figures 1, 2, 4 and 5 are not clear. While the specification has been amended to more accurately reflect what is described in the Figures, there are still deficiencies.

Applicant asserts that labels on the axis for Figures 1 and 2 are not required because the description of the Figure in the specification is clear. Applicant's arguments have been fully considered, but are not found persuasive. There is no indication of units for the Y-axis which makes evaluation of the data presented therein confusing. Units of what is being measured is necessary for making a proper evaluation of the data.

Additionally, Figure 2 cannot be evaluated because there is no distinction between the kontrolle and SAM-6 as the bars of both are open. It is not clear which bar corresponds to which condition. Furthermore, the description in the specification for the X-axis does not make sense with the X-axis of the figure. The description in the Specification refers to LDL fractions being oxidized to different degrees, but the X-axis is labeled as 0, 3 and 15 hours. Therefore, the description of what is being shown in Figure 2 is not clear.

The Specification has been amended to refer to Figure 4 and 5 as showing the result of Sudan III staining. The description of Figure 4 states that the figure "shows cells that were incubated for 48 h with either SAM-6 or an IgM control antibody". However, Figure 4 is a single view - for this Figure to be a comparison, there would need to be 2 views or some distinction in color of staining. Since the figure is in black and white, it is not clear if color was intended. The description of this figure implies that there is red staining, but again, the figure is in black and white.

The amendment for reference to Figure 5 was incomplete in that the text now reads "For the stains shown in Figure 9 Figure 5". Applicant may wish to consider further amendment to this portion of the text as there is no Figure 9 in the instant application."

Applicants allegations on pp. 9-11 of the Response of 7/23/10 have been considered and are not found persuasive.

Applicants would have the Office believe that in the absence of any units assigned to the Y axis, the ordinary artisan would understand that because of the height of the bars between the test and control samples, that this is sufficient to show changes were observed.

Response to Arguments

Neither the examiner nor the ordinary artisan is enabled by the alleged descriptions in the specification for interpreting the meaning of a difference in the bar heights between the sample and control. Accordingly, it is unclear if these differences

are logarithmic, scaled by units of for example, 5, 10 15, etc. What is the statistical significance for any of these comparisons? Applicants are requested to provide new figures and/or amended figure legends with the axes properly labeled and units clearly identified for each figure. Correction is required.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

15. The rejection of Claims 27-32, 34-43 and 48-51 (and new Claims 52-54) under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for any antibody with binding specificity for "at least one of LDLs and oxidized LDL" and having the following structural properties: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or less than the full complement of VL CDR1-3 and VH CDR1-3.

The rejection was set forth in the Office Action of 7/23/09 as follows:

> "Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.
>
> Nature of the Invention/ Skill in the Art
>
> The claims are interpreted as broadly encompassing of an antibody or antigen binding fragment thereof with binding specificity for LDL or oxidized LDL, and where the antibody has: at least 75%, 80%, 85%, 90% or 95%

identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3 from SEQ ID NO:1 and/or SEQ ID NO:3.

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure in the Specification

The specification discloses a single isolated antibody, SAM-6 and sometimes called SAM-6.10, which binds LDL and oxidized LDL. At the time of filing, Applicant's specification did not reveal the structural identity of the antigen but generally characterized the antigen as LDL or oxidized LDL and the ability of the antibody to bind these LDL molecules was measured by an ELISA assay (page 14 of the specification). The sequence for the antibody (SAM-6 and/or SAM-6.10) is disclosed for VL and VH (SEQ ID NO:1 and 3, respectively). The antibody was shown to reduce LDL levels in vivo (Experiments 1 and 2, although no data is provided since the Figures which are discussed in the Specification are not present in the Application).

The specification contemplates but does not specifically disclose working embodiments for just any of the antibody structures encompassed by the claims much less that any modified antibody would have the required properties of binding LDL or oxidized LDL or complementary carbohydrate structures since no actual structure of the specific antigen is provided.

Without sufficient guidance in the written description alone, the ordinary artisan could not practice making and using the myriad antibody embodiments encompassed by the claims because the specification and claims do not define which regions and domains are subject to variation, which regions or domains could tolerate the introduction of the variation, or the nature and extent of the variation. For example, the claims are not limited to whether the extent of variation comprises amino acid substitutions, insertions, deletions and combinations thereof so that the ordinary artisan could predict which variation would not compromise antigen binding specificity. The claims are not limited as to whether the variation occurs in the antigen binding domains or Fc regions, or the CDRs and/or framework domains. Thus it is not readily apparent from the specification or the original claims as filed, how the ordinary artisan could practice the invention without incurring undue experimentation in order to identify a reasonable number of working embodiments based on the extent of antibody variation encompassed by the claims. Further, the claims encompass antibody embodiments having structures that are generally viewed in the field of art as being non-operative or at least unpredictable as to their antigen affininty, namely, antibodies having single variable domains or those having fewer than the full complement of both VL and VH CDRs. Thus the ordinary artisan could not reduce to practice the myriad embodiments and expect to obtain a reasonable number of working embodiments absent undue experimentation at the levels of gene manipulation, antibody screening and bioassay performance.

Prior Art Status: Single CDR-domain Antibodies

The claims encompass isolated antibodies comprising a single CDR domain (and less than the full complement of VH/VL CDRs) from SAM-6 antibody. Applicants have not shown that any isolated any antibody comprising less than a full complement of VH/VL CDRs from a parent SAM-6 antibody of SEQ ID NO:1 and 3 would retain the antigen binding to the LDL and oxidized LDL tested. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework residues influence binding.

MacCallum et al. (J. Mol. Biol. 262:732-745 (1996)) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

de Pascalis *et al.* (Journal of Immunology 169, 3076-3084 (2002)) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (BBRC 307, 198-205, (2003)) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (J. Mol. Biol. 320, 415-428 (2002)) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* (Mol. Immunol. 44: 1075-1084 (2007)) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. 293, 865-881 (1999)) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. 294, 151-162 (1999)) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH CDRs and VL CDRs).

Analyzing applicants own disclosure, which while it does contemplates divergent CDR residues, the only working example is the SAM-6 antibody having heavy chain CDRs paired with complementary light chain CDRs. Additionally, the data indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no examples of mixing or matching of the light chain CDRs or heavy chain CDRs and most importantly there is no working example of placing a single CDR domain of a heavy chain and/or a light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass antibodies comprising VH domains, VL domains and CRDs which vary in the extent to which they resemble the corresponding domain in the parent SAM-6 antibody of SEQ ID NO:1 and 3. This variation can comprise any number and kind of amino acid substitutions. It is not well established in the art that all variable domains are amenable to modifications much less that that substitutions are for conservative amino acids. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al.* (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects and demonstrate that any conservative substitution within any CDR cannot be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

Prior Art Status for Single Variable Domain Antibodies

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))."

The rejection was maintained in the Office Action of 3/23/10 as follows:

"Applicant argues at page 12 of the response that the proper standard for enablement is whether one skilled in the art could make and use the invention without undue experimentation and that the claims are analogous to Wands, where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation. Applicant's arguments have been fully considered, but are not found persuasive.

The production techniques involved in making the claimed antibodies comprising any variation of the antibody variable domains and retaining the binding characteristics for the antigen of interest and common to the specifically produced antibody of SEQ ID NO:1 and 3, are not even remotely related to the production techniques involved in making and screening the monoclonal antibodies of Wands' invention. In Wands, the antibody production and screening of the monoclonal antibodies occurred prior to 1981. The technology used by Wands involved generating a panel of highly specific IgM Mabs against a single known antigen, HbsAg. In 1981, Wands did not even contemplate systems for calculating a) variable domain modifications, and b) amino acid frequency alignment, much less the technology to produce recombinant antibodies as instantly claimed. Wands' only assay for screening the monoclonal antibodies was a commercially available radioimmunoassay kit, and further screening to select IgM isotype and binding affinity constant for the monoclonal antibodies. This is in distinct contrast to the instantly claimed

antibodies. The SAM-6.10 antibody of the instant application has the amino acid sequence of SEQ ID NO:1 and 3 (heavy and light chains). The antigen to which this defined antibody binds is not described in the specification. The specification teaches that this antibody binds to LDL cholesterol or oxidized LDL cholesterol and the instant claims are directed to variant antibodies which also bind LDL cholesterol and oxidized LDL cholesterol. This is in no way similar to the invention and methods of Wands which provided a reproducible method to arrive at the claimed invention. In the instant situation, the antigen to which the disclosed antibody was raised is not provided, nor is there a reproducible method for making the disclosed antibody. Therefore, one cannot follow the methods provided in the instant specification or even the methods in Wands to arrive at the claimed invention and the fact pattern in Wands is not the same as that in the instant application.

Further, Applicant has ignored the Wands Court discussion of what constitutes a "reasonable" number of working embodiments. Wands does not provide any guidance as to what a reasonable number of working examples should be and Applicant's reliance on the Wands decision in the instant case does not appear to appreciate any of the techniques required to produce the instantly claimed antibodies at the time the application was filed. Because the antigen to which the antibody of SEQ ID NO:1 and 3 was raised is unknown, because the molecule to which the antibody of SEQ ID NO:1 and 3 is variable and because the methods which are required to produce variants of an antibody are unpredictable and not disclosed, the experimentation required to make the claimed molecules would be undue and not routine as alleged by Applicant.

Applicant asserts at page 12 of the response that claims where no antibody has ever been produced are routinely granted by the Patent Office, therefore knowledge of antibody structure or predicting the effects of particular variations on antibody binding is not required to satisfy the enablement requirement. Applicant's argument has been fully considered, but is not found persuasive. First, the Examiner is not permitted to comment on the prosecution in other patent applications. Second, Applicant has not provided a single example of any such antibody patent issued by the Office and to which they have privileged access to the prosecution proceeding in order to advance the assertion that claims to any modified antibody are enabled. Such an assertion with no evidence is purely argumentative.

Applicant argues at page 13 of the response that the Patent Office cannot insist that Applicants demonstrate enablement by a particular methodology. Applicant's argument has been fully considered, but is not found persuasive. The rejection is one of lack of enablement and one of the considerations for enablement is predictability in the art. The art is highly unpredictable and the teachings in the instant specification and the prior art do not make up for this deficiency. The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

At page x of the response, Applicant argues that Exhibit A (Boder et al. Proc. Nat't Acad. Sci. USA 97: 10701, 2000) describes directed evolution of scFV fragments and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody. Applicant's argument has been fully considered, but is not found persuasive. In Boder, a single known parent antibody against a known antigen was mutagenized and assayed for binding. Here the skilled artisan would be required to test numerous and indefinite numbers of antigens as not all HDL and LDL is the same in order to find an antigen to which both the purified and disclosed antibody could bind as well as finding an antibody which has the required amino acid sequence similarity that is being claimed. The unduly burdensome amount of experimentation to screen all possible antigens and antibodies and characterize these antibodies would not fall within what Wands considers routine experimentation."

Applicants allegations on pp. 11-13 have been considered and are not found persuasive.

a) Applicants allege exhibit B shows scfv comprising SEQ ID NOS 1 and 3 and a single variable antibody comprising VH of SEQ ID NO:3 bind apoB100 of LDL and oxLDL. Applicants allege the binding for the SAM6 antibody is specific for apoB100 found in both LDL and oxLDL.

Response to Arguments

Initially, the examiner submits that the extrinsic evidence presented in Exhibit B is of the nature and kind that is required to be entered by declaration under 37 CFR 1.132.

"When any claim of an application or a patent under reexamination is rejected or objected to, any evidence submitted to traverse the rejection or objection on a basis not otherwise provided for must be by way of an oath or declaration under this section. [48 FR 2713, Jan. 20, 1983, effective Feb. 27, 1983; revised, 61 FR 42790, Aug. 19, 1996, effective Sept. 23, 1996; revised, 65 FR 54604, Sept. 8, 2000, effective Sept. 8,2000; revised 65 FR 57024, Sept. 20, 2000, effective Nov. 29, 2000]."

Accordingly, the document has not been considered and has been placed in the application file.

b) Applicants allege Exhibit A ((Boder et al., Proc. Nat'l Acad. Sci. USA 97:10701 (2000)) of record corroborates that variant antibodies that bind to LDL or oxLDL could be readily produced without undue experimentation; and SEQ ID NOs: 1 and 3 may be used as a blueprint to produce a limited number of SEQ ID NOs: 1 and/or 3 variants with the benefit of substantial antibody structure and function knowledge and location of predicted CDRs, and which can be verified to LDL or oxLDL using a routine assay.

Response to Arguments

Initially it is noted that the claim language requires the ability of any antibody having a VH and VL of SEQ ID NOS: 1 and 3 much less any variants thereof to bind "to at least one of low density lipoproteins (LDL) and oxidized LDL (oxLDL)", which in plain language, is not at all clear what component(s) of the structure shared between LDL and oxLDL is contemplated as being bound.

For brevity, the attached article (Teerlink et al. (J. Lipid Res. 45:954-966 (2004)) provides a list of at least the following lipid components in an LDL particle as follows: cholesteryl ester; free cholesterol (FC), FC in the core compartment of LDL, FC in the surface components of LDL, phospholipid, triglyceride. The reference does not discuss the proteins found in LDLs and amongst which include ApoB and ApoB100. The attached article by McNamara et al (J. Lipid Res. 37:1924-1935 (1996)) suggests the complexity of what an LDL means. For example, McNamara explores the subspecies of LDLs where differences are attributable to lipid composition profiles and conformational changes in ApoB. Here the ordinary artisan would readily understand that Applicants had not enabled the species of antibodies where the identity of the epitope for the SAM6 antibody from which the VH/VL of SEQ ID NOS: 1 and 3 are obtained much less for the genus of variants that they envisage in the claims.

Applicants have not established that the ordinary artisan could reasonably predict much less screen the genus of antibody variants for SEQ ID NO: 1 and 3 having the ability to bind to any component(s) on either LDL and/or oxLDL absent undue experimentation. This is because Applicants themselves have not and cannot

demonstrate the specificity and exclusivity for the genus of antibodies having all of the required properties of the claims. Even, assuming *arguendo*, the genus of antibodies was able to bind all of the components of an LDL or oxLDL, the question remains whether the binding is specific or cross-reactive for amongst the recognized components. By any interpretation of the *Wands* factors, Applicants disclosure is not enabling for the genus of antibodies encompassed by the claim scope. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19, 24 (CCPA 1970). "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" *Genentech, Inc. v. Novo Nordisk*, A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)).

Finally, while Applicants urge the Office to believe that because SEQ ID NOS: 1 and 3 are the holy grail or blueprint for the ordinary artisan from which to begin designing new variants, Applicants have not even shown the critical residues in the CDRs and frameworks that are required consensus sequences from those which are amenable to modification. A factor in the analysis under Wands is what constitutes undue experimentation. The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Dufner (Trends Biotechnol. 24(11):523-29 (2006)) teaches: “specific structural information - on the antibody to be

optimized, its antigen and their interaction- is rarely available or lacks the high resolution required to determine accurately important details such as side-chain conformations, hydrogen-bonding patterns and the position of water molecules" (p. 527, Col. 2, ¶1). Applicants specification and the evidence of record does not define specific structural information detailing the number of and exact position of hotspots in the CDRs which "can vary considerably from case to case and therefore cannot be predicted" (legend to Figure 2 of Dufner). Thus even with the availability of screening approaches as taught in the specification and Dufner, the ordinary artisan could not predict the hotspots much less those residues critical for conferring specific antigen binding for any of the claimed CDRs absent further additional information and experimentation. What does a sequence alignment for the CDRs/FRs look like for a "reasonable" number of antibodies that would guide the ordinary artisan in determining the important common shared or similar binding residues that confer specific antigen binding? Are any hotspots present in the CDRs and frameworks, what is the frequency of those hot spots and what are the positions of those hot spots?

The rejection is maintained.

New Grounds for Objection

Sequence Listing/ Specification

New Matter

16. The amendment to the specification in the Response of 7/23/10 to change the sequence for the VH CDR3 domain from residues "Lys-Thr" to "Arg-Pro" constitutes

new matter. The Sequence Listing of 5/11/06 recites the original residues for SAM 6 VH ("Lys-Thr") and does not support the amendment.

Applicants revised Sequence Listing of 7/23/10 does not rectify the absence of original written description support for the amendments to SEQ ID NOS: 3 and 4. Applicants have not provided any explanation why residues 106 and 107 have been corrected to amend the VH CDR3 domain from residues "Lys-Thr" to "Arg-Pro" in the Response of 7/23/10.

Applicants allege on p. 7 of the Response of 7/23/10, that support for the VH sequence is shown on p. 13, lines 8-96 of the specification. However, the Examiner's search of this page amongst all of the other pages does not identify support for this amendment. The only support in the specification for "Arg-Pro" is in the SAM6 VL CDR2 domain.

This is a new matter objection for both the specification and revised Sequence Listing.

Specification

17. The amendment to the specification to enter the name and address of depository in addition to the date of hybridoma deposit has not been entered. Applicants' submission of a statement by Frank Hensel dated 4/18/08 in the absence of a deposit receipt is not found to be relevant to this proceeding. The statement makes no reference to a hybridoma for the SAM6 antibody. On its face, the Declarant's statement

is confusing and seemingly irrelevant. Perhaps there is a loss in the translation which can be remedied by Applicants attorney.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description/ New Matter

18. Claims 43 and 52-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 43 and 52-54 are interpreted as being drawn to the VH CDR3 of SEQ ID NO:3 having the following sequence: “Asp-Arg-Leu-Ala-Val-Ala-Gly-Arg-Pro-Phe-Asp-Tyr (CDR3) SEQ ID NO:3.”

The examiner’s search of the specification for the limitation does not identify literal support for this limitation. (MPEP 706.03(m) states in part "New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See MPEP § 608.04 to § 608.04(c). See In re

Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) and MPEP § 2163.05 for guidance in determining whether the addition of specific percentages or compounds after a broader original disclosure constitutes new matter.")

This is a new matter rejection.

New Grounds for Rejection

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 27-32, 34-42 and 48-54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 73, 80, 81, 106-112, 115, 116 and 122-124 of copending Application No. 10/579,290 (US 20080108133). Although the conflicting claims are not identical, they are not patentably

distinct from each other because the claims recite the same sequenced for the VH and VL domains of the claimed antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Art Unit 1643
Primary Examiner